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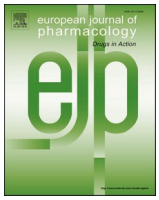

The therapeutic potential of resolvins in pulmonary diseases

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ABSTRACT

Uncontrolled inflammation leads to nonspecific destruction and remodeling of tissues and can contribute to many human pathologies, including pulmonary diseases. Stimulation of inflammatory resolution is considered an important process that protects against the progression of chronic inflammatory diseases. Resolvins generated from essential omega-3 polyunsaturated fatty acids have been demonstrated to be signaling molecules in inflammation with important pro-resolving and anti-inflammatory capabilities. By binding to specific receptors, resolvins can modulate inflammatory processes such as neutrophil migration, macrophage phagocytosis and the presence of pro-inflammatory mediators to reduce inflammatory pathologies. The discovery of these pro-resolving mediators has led to a shift in drug research from suppressing pro-inflammatory molecules to investigating compounds that promote resolution to treat inflammation. The exploration of inflammatory resolution also provided the opportunity to further understand the pathophysiology of pulmonary diseases. Alterations of resolution are now linked to both the development and exacerbation of diseases such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, acute respiratory distress syndrome, cancer and COVID-19. These findings have resulted in the rise of novel design and testing of innovative resolution-based therapeutics to treat diseases. Hence, this paper reviews the generation and mechanistic actions of resolvins and investigates their role and therapeutic potential in several pulmonary diseases that may benefit from resolution-based pharmaceuticals.

1. Introduction

Inflammation is a physiological protective response aimed against infection and injury of host cells (Nathan and Ding, 2010). Normally, this response is self-limited, and tissues will subsequently restore to their normal functional and structural state. However, when inflammation is insufficiently resolved, this may lead to undesirable chronic inflammation and tissue fibrosis. A disproportionate and chronic inflammatory response is implicated to play a fundamental role in many diseases ranging from rheumatoid arthritis, asthma, multiple sclerosis, inflammatory bowel disease and even Alzheimer's disease and cancer.

Currently, treating excessive inflammation is primarily based upon the inhibition of pro-inflammatory mediators driving acute inflammation with drugs such as corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) or immunosuppressive biologics like infliximab (Gilroy and Bishop-Bailey, 2019; Levy, 2012). While these can improve disease symptoms in a subset of patients, they are generally symptomatic treatments that do not cure chronic inflammatory disease and their immunosuppressive effects may lead to predisposition to harmful infections. Additional side effects may also occur such as osteoporosis, increased bleeding, and hyperglycemia (Swartz and Dluhy, 1978; Vonkeman and Van de Laar, 2010). Therefore, there is a need for more effective therapies that efficiently target chronic inflammatory disease with fewer unwanted side effects.

Suppression of inflammation with drugs was in line with the reasoning that the resolution of self-limited inflammation was a passive process (Serhan, 2017). This passive process would involve the gradual degradation of pro-inflammatory mediators such as cytokines and chemokines over time, halting the attraction of circulating immune cells to the site of injury (Blaudez et al., 2022). However, research initiated by Serhan et al. (Serhan et al., 2002; Serhan and Savill, 2005) has led to a paradigm change, showing that resolution of inflammation is an active process instead. The key to this discovery was the identification of resolvins and other specialized pro-resolving mediators (SPMs). Thus far, four families of SPMs have been elucidated. These are resolvins, which are the focus of this review, and marensins, protectins and lipoxins. These pro-resolution molecules modulate certain mechanism that stimulate a pro-resolving response of the immune system to allow reintroduction of homeostasis, such as by modulating cytokine

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Abbreviations

ACE-2	angiotensin converting enzyme 2
ALI	acute lung injury
ALX/FPR2	formyl peptide receptor 2
ARDS	acute respiratory distress syndrome
ASL	airway surface liquid
BAL	bronchoalveolar lavage
BLT_1	Leukotriene B_4 receptor 1
CD	cluster of differentiation
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
$Chemerin_1$	chemerin receptor 1
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
DAMP	damage-associated molecular patterns
DC	dendritic cell
DHA	docosahexaenoic acid
DPA	docosapentaenoic acid
DRV1/GPR32	G protein-coupled receptor 32
DRV2/GPR18	G protein-coupled receptor 18
E. coli	*Escherichia coli*
ENaC	epithelial sodium channel
EPA	eicosapentaenoic acid
GPCR	G protein-coupled receptor
GSK3β	glycogen synthase kinase 3 beta
IL	interleukin
LLC	Lewis lung carcinoma model
LOX	lipoxygenase
LPS	lipopolysaccharide
LTB_4	leukotriene B_4
MCP	monocyte chemoattractant protein
MIP-1β	macrophage inflammatory protein 1-beta
MMP12	matrix metalloproteinase 12
NETs	neutrophil extracellular traps
NF-κB	nuclear factor-κB
NK	natural killer
NO	nitric oxide
NSAID	nonsteroidal anti-inflammatory drug
PAMP	pathogen-associated molecular patterns
PRR	pattern recognition receptor
P. aeruginosa	*Pseudomonas aeruginosa*
PUFA	omega-3 polyunsaturated acid
RvD	D-series resolvin
RvE	E-series resolvin
RvT	T-series resolvin
S1	spike glycoprotein 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SPM	specialized pro-resolving mediator
STAT3	signal transducer and activator of transcription 3
TGF-β	transforming growth factor-β
Th2	T-helper 2
TLR	Toll-like receptor
TNF-α	tumor necrosis factor alpha
TRP	transient receptor potential

expression (Blaudez et al., 2022). SPMs are regarded as non-immunosuppressive and may even improve the destruction and clearing of bacteria (Serhan, 2017). Thus, these compounds could deliver novel immunoresolvent therapeutics for the treatment of many inflammatory pathologies and have led to the interest in pharmacological research focused on inflammatory resolution.

Experiments have shown that resolvins play a role in many inflammatory diseases, ranging from peritonitis, obesity, aging, neurological disease, arthritis and more (Serhan and Levy, 2018). Notably, several studies have shown that levels of resolvins may decline during the inflammatory response in pulmonary diseases and that they could serve a role in treating these diseases (Briottet et al., 2020; Croasdell et al., 2015; Hisada et al., 2017; Hsiao et al., 2015; Levy, 2012; Luo et al., 2022; Palmas et al., 2021; Recchiuti et al., 2019). Thus, elucidating the mechanism of resolution and the role of resolvins therein provides the opportunity to improve our understanding of the pathophysiology of pulmonary diseases and can aid in discovering novel therapeutic approaches to improve disease burden. Hence, this review reports current insights on resolvins, inflammation and resolution pathways in pulmonary diseases, and the potential therapeutic application of modulating inflammatory resolution.

2. Acute inflammation and resolution

2.1. The inflammatory response

When exogenous and/or endogenous danger signals caused by chemical, mechanical or biological tissue damages are sensed, the inflammatory induction phase is designed to allow rapid and robust immune activation to shield the host from further harm (Schett and Neurath, 2018; Takeuchi and Akira, 2010). If harmful microbes (bacteria/fungi/viruses) infect and damage host cells, pattern recognition receptors (PRRs) expressed on host cells may detect pathogen-associated molecular patterns (PAMPs) (Takeuchi and Akira, 2010). Furthermore, PRRs may identify damage-associated molecular patterns (DAMPs) released by injured or dying cells either due to trauma or also due to infection (Fig. 1).

Stimulation of PRRs activates intracellular signaling cascades, which can lead to the initiation of innate immunity by promoting the activation of immune cells such as dendritic cells (DCs), monocytes/macrophages, neutrophils, natural killer (NK) cells, mast cells and eosinophils (Gong et al., 2020). Additionally, non-leukocyte cells such as endothelial and epithelial cells can also express these receptors and be activated. Together, these can subsequently release important pro-inflammatory mediators such as cytokines and chemokines to recruit additional inflammatory cells and activate adaptive immunity, which is less commonly activated directly through molecular pattern recognition. Outside of protein mediators, the induction/initiation phase of inflammation is characterized by the production and release of lipid mediators such as leukotrienes and prostaglandins. Prostaglandins mediate the effect of the cardinal signs of inflammation, including vasodilation, which leads to enhanced vascular permeability and edema at the site of inflammation (Funk, 2001). Leukotriene B_4 (LTB_4) is primarily associated with promoting chemotaxis of several immune cells and cysteinyl leukotrienes with increasing vascular permeability which facilitates immune cell diapedesis (Henderson, 1994). Thus, these lipid mediators often act synergistically with other mediators to elicit enhanced immunological responses.

Amidst the initial responders towards the acute inflammatory response, neutrophils exit postcapillary venules and enter the inflammatory site, a process governed by chemoattractants which can be exogenous (microbially derived) and/or endogenous such as chemokines and LTB_4 (Serhan, 2017; Serhan and Levy, 2018). Infiltrated neutrophils can kill invading microbes through phagocytosing them, degranulation, or by generating neutrophil extracellular traps (NETs) (Abdolmaleki et al., 2020). This is followed by the recruitment of monocytes that differentiate into macrophages (Isobe et al., 2012b), which can both induce and sustain inflammatory tissue responses

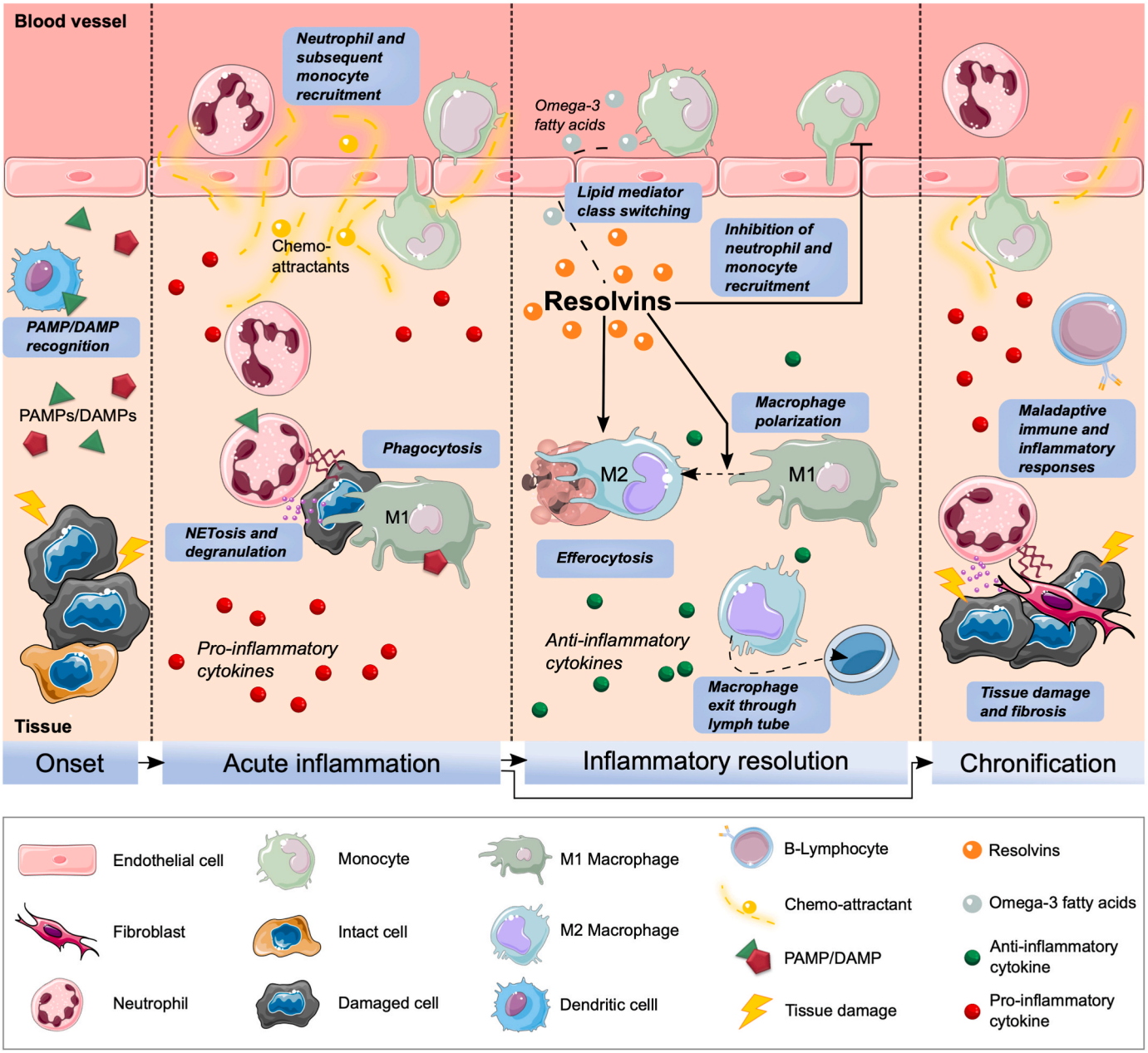

Fig. 1. Overview of the general processes of inflammation and resolution. At inflammatory onset, a noxious stimulus leads to injury of tissue cells, causing the release of damage and pathogen-associated molecular patterns (DAMPs and PAMPs). These can be sensed by tissue resident cells such as dendritic cells and lead to pro-inflammatory signaling. During acute inflammation, microvascular changes and chemoattractants promote the influx of neutrophils followed by monocytes. These leukocytes exert defensive responses that facilitate removing the inflammatory infiltrate such as phagocytosis, degranulation, NETosis and the release of pro-inflammatory cytokines. During the latter part of acute inflammation, lipid mediator class switching occurs, leading to the generation of resolvins and other pro-resolving mediators that halt the inflammatory response. During the resolution phase, macrophages are reprogrammed to an anti-inflammatory phenotype (M1 to M2), apoptotic leukocytes are removed and the influx of leukocytes is inhibited. Primarily macrophages, but also other non-apoptotic immune cell may leave the tissue through reverse migration and/or lymphatics. Ultimately, the tissue will be repaired and returned to homeostasis. However, if resolution is dysregulated and/or the inflammatory source is inadequately removed, chronic inflammation can arise in which pro-inflammatory responses persist that cause ongoing tissue damage and fibrosis (Abdolmaleki et al., 2020; Gong et al., 2020; Isobe et al., 2012b; Schett and Neurath, 2018; Serhan, 2017; Serhan and Levy, 2018; Sugimoto et al., 2019; Takeuchi and Akira, 2010; Uddin and Levy, 2011). This Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

(Abdolmaleki et al., 2020). Although the initiated inflammatory response is protective and meant to restore tissue homeostasis, failure to abolish an excessive microbial load and/or dysfunctional signaling of the immune system can lead to chronic inflammation, ultimately causing degradation and/or remodeling of tissues (Briottet et al., 2020). For instance, when excessive neutrophil infiltration and activation occurs in tissues for a prolonged state, the release of their antimicrobial defense mechanisms can cause significant tissue destruction over time and further amplify inflammation, stimulating chronic inflammatory responses (Serhan and Levy, 2018).

2.2. Resolution phase in inflammation

Normally, the inflammatory response is self-limited and allows the

affected tissue to return to homeostasis due to induction of a resolution phase crucial to ceasing acute inflammation (Uddin and Levy, 2011). The physiological processes involved in the pro-resolution phase are distinct from anti-inflammatory processes. This is based upon pro-resolving mediators not solely blocking pro-inflammatory processes such as granulocyte tissue entry and their activation, but also inducing clearance of debris and inflammatory cells from the affected tissue (Serhan and Savill, 2005). A functional difference between pro-resolving mediators and purely anti-inflammatory mediators is that SPMs induce expedited return to homeostasis without collateral immunosuppression (Uddin and Levy, 2011). To initiate resolution, prostaglandins involved during the initiation phase of inflammation conversely also induce the production of SPMs through activating mRNA translation in host cells of SPM producing enzymes. This process is referred to as lipid mediator class switching, involving a swap from pro-inflammatory leukotriene and prostaglandin production to resolvins and other SPMs with pro-resolving functions (Fig. 1). Inflammatory resolution can be considered a "clean-up" process to restore tissue integrity and is generally considered to be extremely robust (Schett and Neurath, 2018). Thus, most inflammatory processes remain self-limited.

While many processes related to resolution have been discovered in different pathologies, certain universal mechanisms have been identified. Firstly, one key function of resolution is halting neutrophil recruitment towards the affected tissue. SPMs such as resolvin D1 (RvD1) and resolvin E1 (RvE1) can block this recruitment (Gilroy and Bishop-Bailey, 2019; Liu et al., 2022), for example by downregulation of C-X-C chemokine receptor 2 which halts neutrophil activation by substances such as LTB_4 (Schett and Neurath, 2018). Other important aspects of resolution include the removal of dead neutrophils and inducing a macrophage transition from a pro-inflammatory phenotype towards a pro-resolving one. These key aspects are all regulated by the generation of resolvins and other SPMs (Gilroy and Bishop-Bailey, 2019; Liu et al., 2022; Serhan and Savill, 2005). Many other important functions of resolvins have been reported, including promoting the scavenging of pro-inflammatory factors, inducing tissue healing and alleviating inflammatory pain (Liu et al., 2022; Sugimoto et al., 2016). The ability of resolvins to effectively restore tissue homeostasis after inflammation indicates that these lipid mediators play a crucial role in the resolution of inflammation and preventing chronic disease.

3. Resolvin biosynthesis and their targets

3.1. Endogenous production of resolvins

Resolvins were first discovered by Serhan et al. (2002) while performing a lipidomic analysis of murine air pouch exudates to elucidate endogenous bioactive lipids derived from omega-3 fatty acids. Before their discovery, animal and human studies had shown that supplementation with the omega-3 polyunsaturated acids (PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) had positive effects on treating multiple chronic diseases such as atherosclerosis and cardiovascular disease but lacked clear understanding of underlying mechanisms before SPMs were elucidated. The lipid mediators prostaglandins, leukotrienes and lipoxins are generated from the omega-6 fatty acid arachidonic acid by enzymatic metabolism (Uddin and Levy, 2011). Resolvins (E-, D- and T-series) on the other hand are produced from the omega-3 PUFAs (Table 1) (Liu et al., 2022). The E-series resolvins are derived from EPA, D-series from DHA, and T-series from docosapentaenoic acid (DPA) by enzymatic reactions such as through lipoxidase (LOX) and endothelial cyclooxygenase (COX) at the inflammatory sites, often involving transcellular biosynthesis.

The synthesis of E-series resolvins (RvE1-RvE4) typically occurs by leukocytes such as neutrophils together with endothelial cell enzymatic actions (Liu et al., 2022). Acetylated COX-2 or cytochrome P450 metabolizes EPA to its 18R-hydroxyeicosapentaenoic acid (18R-HEPE) derivative, which is then further metabolized by 5-LOX to a 5(S),6-epoxy intermediate (Fig. 2) (Liu et al., 2022; Serhan et al., 2022). This intermediate can subsequently be hydrolyzed ultimately to RvE1 or reduced to RvE2. While COX-2 acetylation is often induced by aspirin, other agents have been shown to facilitate this reaction. Alternatively, RvE3 can be produced from EPA by 15-LOX in eosinophils (Recchiuti et al., 2019). The more recently discovered RvE4 is proposedly synthesized through EPA conversion to 15S-H(p)EPE by 15-LOX followed by conversion to the RvE4 precursor 15S-hydroxy-5S-HpEPE by 5-LOX which can then be converted to RvE4 by peroxidase activity (Liu et al., 2022). D-series resolvins (RvD1-RvD6) are synthesized by two different pathways, generating the 17R- and 17S-series resolvins. The 17R series are formed through acetylated COX-2 and 17S resolvins by 15-LOX. The 17S series appear predominant during the absence of aspirin (Serhan et al., 2002). RvD1 and RvD2 are produced through a 7(8)-epoxide intermediate by 5-LOX. RvD3 to RvD6 are generated by formation of a 4 (5)-epoxide intermediate through 5-LOX followed by subsequent enzymatic activity (Serhan et al., 2022).

The production of T-series resolvins (RvT1-RvT4) require conversion of DPA to 13R-hydroxy-DPA via endothelial COX-2 and a subsequent reduction (Liu et al., 2022). Neutrophils can produce 7-hydroxy-13R-hydroxy-docosapentaenoic acid from 13R-hydroxy-DPA, which can form RvT4 after reduction of the hydroperoxy-group (Rodriguez and Spur, 2020). RvT4 can then subsequently be transformed to RvT1 by enzymatic lipoxidase. Alternatively, an allylic epoxide of 7-hydroxy-13R-hydroxy-docosapentaenoic acid can be enzymatically hydrolyzed into RvT2 and RvT1. The production of RvTs can be enhanced with statins by S-nitrosylation of COX-2 (Serhan and Levy, 2018).

3.2. Receptor targets of resolvins

While many resolvin subtypes exist (Table 1), they all exert their biological functions due to interaction with G protein-coupled receptors (GPCRs) (Abdolmaleki et al., 2020). RvE1 and RvE2 bind to chemerin receptor 1 ($Chemerin_1$; formerly ChemR23) expressed on DCs and monocytes/macrophages to stimulate phagocytosis of apoptotic neutrophils. RvE1 has also been associated with preventing osteoclast-initiated bone damage (Serhan et al., 2022). Additionally, RvE1 attenuates neutrophil infiltration and inhibits cytokine production (Luo et al., 2022). Aside from $Chemerin_1$, RvE1 and RvE2 can antagonistically bind to the LTB_4 receptor 1 (BLT_1) which can increase apoptosis of neutrophils, reduce neutrophil chemotaxis and increase efferocytosis by macrophages (Blaudez et al., 2022). In humans, these receptors are predominantly expressed by eosinophils, neutrophils, macrophages, DCs and effector T cells (Uddin and Levy, 2011). Both receptor BLT_1 and $Chemerin_1$ can be co-expressed with nociceptive transient receptor potential (TRP) channels in which studies have shown an analgesic effect of RvE1 through TRPV1 inhibition (Roh et al., 2020). The receptors for RvE3 and RvE4 have thus far not been well documented (Li et al., 2020), although there is evidence that RvE3 may also antagonistically bind to BLT1 (Sato et al., 2019). Reported function of RvE3 include reducing the chemotaxis of neutrophils and inhibiting cytokine production such as interleukin 23 (IL-23) and IL-17A. RvE4 has been described to lead to efferocytosis of both apoptotic neutrophils and senescent erythrocytes (Serhan et al., 2022).

Resolvin D1 can bind with high affinity to the formyl peptide receptor 2 (ALX/FPR2) (Abdolmaleki et al., 2020), expressed greatly on monocytes, neutrophils and inflammatory activated macrophages (Blaudez et al., 2022). Activation of ALX/FPR2 is associated with switching of macrophages towards a pro-resolving phenotype and reduces chemotaxis of neutrophils. Furthermore, RvD1 may bind with G protein-coupled receptor 32 (GPR32), resulting in downregulation of inflammatory chemoattractants by monocytes, neutrophils, and macrophages. GPR32 activation may also induce macrophage polarization from a pro-inflammatory (M1) to a pro-resolutive phenotype (M2). While ALX/FPR2 is mainly seen in neutrophils and monocytes, GPR32 is highly expressed on macrophages (Li et al., 2020). Both ALX and GPR32

Table 1
Overview of precursors and receptor targets of resolvin subtypes and their general actions in various disease models.

Subtype	Main precursor	Receptor target	General functions	References
RvE1	EPA	Chemerin$_1$, BLT$_1$	– Inhibit neutrophil recruitment – Stimulate apoptotic neutrophil phagocytosis – Prevent osteoclast induced bone damage – Inhibit pro-inflammatory cytokine production – Increase efferocytosis by macrophages – Induce clearance of eosinophils by regulating natural killer cells trafficking – Stimulate SPM lipoxin A$_4$ generation – Attenuate endothelial cell senescence – Promote tumor debris clearance – Accelerate wound healing – Antimicrobial activity – Antidepressant effects in murine lipopolysaccharide depression model – Reduce neurological pain	(Abdullatif et al., 2022; Arita et al., 2005, 2007; Deyama et al., 2018b; Hasturk et al., 2006; Haworth et al., 2008, 2011; Herova et al., 2015; Herrera et al., 2015; Menon et al., 2017; Quiros et al., 2020; Roh et al., 2020; Schwab et al., 2007; Seki et al., 2010; Shamoon et al., 2022; Sulciner et al., 2017; Xu et al., 2010)
RvE2	EPA	Chemerin$_1$, BLT$_1$	– Induce phagocytosis of apoptotic neutrophils – Inhibit neutrophil chemotaxis – Stimulate efferocytosis by macrophages – Inhibit production of pro-inflammatory interleukins – Antidepressant effects in murine lipopolysaccharide depression model	(Deyama et al., 2018b; Oh et al., 2012; Sato et al., 2019; Tjonahen et al., 2006)
RvE3	EPA	BLT$_1$ (?)	– Inhibit the chemotaxis of polymorphonuclear leukocytes – Reduce pro-inflammatory cytokine – Stimulate efferocytosis by macrophages – Antidepressant effects in murine depression – Improve insulin sensitivity and glucose tolerance – Reduce incidence of preterm birth	(Deyama et al., 2018a; Isobe et al., 2012a; Sato et al., 2019; Shimizu et al., 2022; Yamashita et al., 2013)
RvE4	EPA	–	– Induce efferocytosis of apoptotic neutrophils and senescent erythrocytes	(Libreros et al., 2020; Norris et al., 2019; Serhan et al., 2022)
RvD1	DHA	ALX/FPR2, DRV1/GPR32	– Inhibit the chemotaxis of neutrophils – Induce macrophage switching to a pro-resolving phenotype (M1 to M2) – Reduce production of chemoattractants by leukocytes – Inhibit osteoclast recruitment and activation – Decrease in pro-inflammatory cytokines – Increase/mediate anti-inflammatory cytokine effects – Improve glucose tolerance and insulin sensitivity – Delay onset of fibrosis in myocardial infarction model – Promote tumor debris clearance – Promote wound healing – Antidepressant effects in murine depression – Stimulate regulatory T-cell differentiation – Alleviate neuropathic pain – Enhance phagocytosis of *E. coli*	(Bang et al., 2010; Benabdoun et al., 2019; Cheng et al., 2021; Deyama et al., 2017; Hellmann et al., 2011; Hong et al., 2003; Kain et al., 2015; Kang and Lee, 2016; Krishnamoorthy et al., 2010, 2012; Li et al., 2014; Liu et al., 2022; Menon et al., 2017; Norling et al., 2012; Roh et al., 2020; Schmid et al., 2016; Sulciner et al., 2017; Titos et al., 2011; Vasconcelos et al., 2015; Wang et al., 2011; Xu et al., 2010)
RvD2	DHA	DRV2/GPR18	– Induce M1 to M2 macrophage differentiation – Decrease cytokine production – Stimulate nitric oxide production – Analgesic effect in neuropathic pain – Stimulate regulatory T-cell differentiation – Inhibit neutrophil recruitment – Stimulate myogenesis – Antidepressant effects in murine depression – Improve wound healing – Induce macrophage release of pro-myogenic factors	(Chiang et al., 2015, 2017; Chiurchiu et al., 2016; Croasdell et al., 2015; Deyama et al., 2017; Dort et al., 2021; Menon et al., 2017; Roh et al., 2020; Spite et al., 2009; Suzuki et al., 2021)
RvD3	DHA	ALX/FPR2, DRV1/GPR32	– Stimulate phagocytosis of microbial particles and efferocytosis – Increase anti-inflammatory cytokines	(Arnardottir et al., 2016; Dalli et al., 2013; Gilligan et al., 2019; Lee et al., 2020; Serhan, 2014; Serhan et al., 2002)

(*continued on next page*)

Table 1 (*continued*)

Subtype	Main precursor	Receptor target	General functions	References
			– Decrease pro-inflammatory cytokines – Reduce neutrophil migration – Inhibit pain – Stimulate tumor debris clearance	
RvD4	DHA	–	– Stimulate nonphlogistic macrophage recruitment – Decrease neutrophil chemotaxis and NETosis – Increases clearance of apoptotic cells by fibroblasts – Stimulate leukocyte apoptosis – Increase DHA-derived SPM production	(Cherpokova et al., 2019; Winkler et al., 2016, 2018)
RvD5	DHA	DRV1/GPR32, GPR101	– Stimulate phagocytosis of *E. coli* – Inhibit neuropathic and inflammatory pain in male but not female *in vivo* models – Increase regulatory T-cell differentiation – Inhibit osteoclast formation – Decreased Th17 cell differentiation	(Baggio et al., 2023; Chiang et al., 2012; Flak et al., 2020; Luo et al., 2019; Yamada et al., 2021)
RvD6	DHA	–	– Implicated in myofiber regeneration – Promote wound healing and nerve regeneration (cornea) – Reduced pro-inflammatory cytokines	(Markworth et al., 2021; Pham et al., 2020, 2021)
RvT1	DPA	–	– Limit neutrophil infiltration – Reduce inflammasome activation – Reduce NETosis – Decrease bacterial titer	(Chiang et al., 2022; Dalli et al., 2015)
RvT2	DPA	–	– Inhibit inflammasome response – Stimulate NET-phagocytosis – Reduce bacterial load – Reduce infiltration of neutrophils	(Chiang et al., 2022; Dalli et al., 2015)
RvT3	DPA	–	– Limit neutrophil infiltration – Reduce inflammasome activation – Reduce NETosis – Decrease bacterial titer	(Chiang et al., 2022; Dalli et al., 2015)
RvT4	DPA	–	– Inhibit inflammasome response – Reduce bacterial load – Increase NET-phagocytosis – Reduce infiltration of neutrophils	(Chiang et al., 2022; Dalli et al., 2015)

Abbreviations: DPA, docosapentaenoic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

are also expressed in T-cells and studies have shown that RvD1 can induce regulatory T cell differentiation through GPR32 (Ferreira et al., 2022; Li et al., 2020). Resolvin D2 binds to DRV2/GPR18 and can, similarly to RvD1, stimulate macrophage M1 to M2 polarization (Briottet et al., 2020). Other functions include reducing cytokine production and stimulating nitric oxide (NO) production, thereby reducing endothelial-leukocyte interactions (Briottet et al., 2020; Recchiuti et al., 2019). Additionally, RvD2 has been shown to stimulate the release of pro-myogenic factors by macrophages and directly stimulate myogenesis in myogenic cells through GPR18 (Dort et al., 2021). Similar to RvE1, RvD1 and RvD2 alleviate neuropathic pain through TRP channel inhibition, with RvD1 inhibiting TRPA1, TRPV3 and TRPV4 while RvD2 inhibits TRPV1 and TRPA1 (Roh et al., 2020).

While RvD5 also binds to GPR32 and RvD3 binds to both GPR32 and ALX/FPR2, the receptors for RvD4 and RvD6 have not been documented (Arnardottir et al., 2016; Li et al., 2020). Recently, RvD5 has been revealed to additionally activate GPR101 expressed on macrophages (Chiang and Serhan, 2020). RvD5 and RvD1 were shown to enhance phagocytosis of *Escherichia coli* (*E. coli*), reducing bacterial loads and enhancing the effect of the antibiotic ciprofloxacin all while reducing the time to reach resolution (Serhan et al., 2014). Similarly, RvD3 has been shown to stimulate the uptake of microbial particles through GPR32. Additionally, RvD3 decreases IL-6 production, increases IL-10 and decreases neutrophil chemotaxis. In vitro thrombus studies indicate that RvD4 accelerates resolution through decreasing neutrophil infiltration, stimulating nonphlogistic monocytes recruitment and increasing leukocyte apoptosis (Cherpokova et al., 2019). Metabolipidomics revealed that RvD6 reduces in aged mice muscle among other SPMs, indicating that they may play a role in age related dysfunction of myofiber regeneration (Markworth et al., 2021). Within D-series resolvins, the 17R series generally show greater pro-resolving actions at equal dosing compared to 17S epimers, with 17R-RvD1 showing decreased rate of metabolic inactivation by lung macrophages and greater half-life *in vivo* compared to 17S-RvD1 (Levy, 2012). Between D-series and E-series this distinction is less clear and appears to depend on the pathology and/or disease model. For example, neutrophil migration assays and wound healing studies in mice indicate RvE1 superiority at inhibiting neutrophil migration and stimulating wound healing compared to RvD1 and RvD2 (Menon et al., 2017). Conversely, *in vivo* models of *Pseudomonas aeruginosa* infection revealed that unlike RvD1, oral gavage with RvE1 did not significantly reduce the infection (Codagnone et al., 2018).

The targets of RvTs have been less documented, however, similar functions as other resolvin subtypes have been discovered. RvTs have shown to limit infiltration of neutrophils, decrease bacterial load, regulate inflammasome components, reduce the formation of NETs and increase NET clearance by macrophages (Chiang et al., 2022; Serhan and Levy, 2018). Of these, RvT2 was most potent at increasing NET-phagocytosis (Chiang et al., 2022).

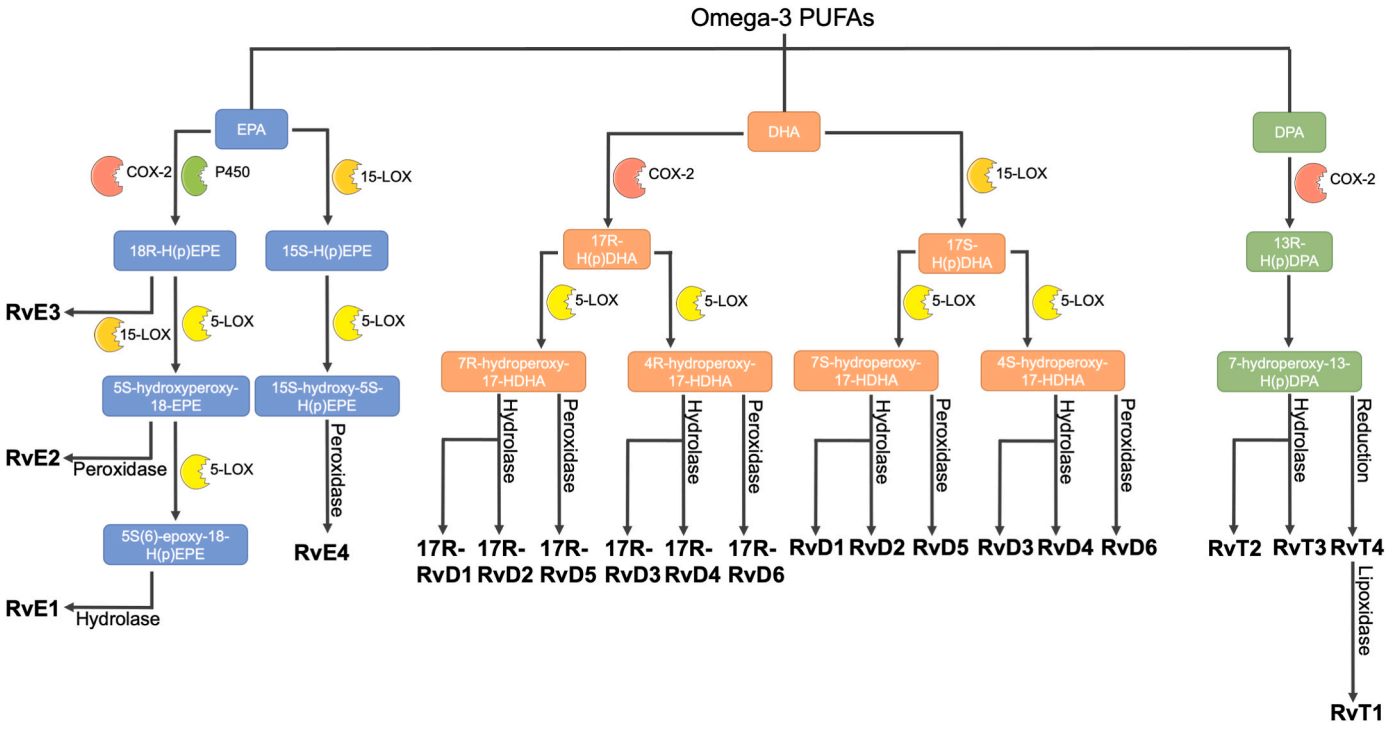

Fig. 2. The biosynthesis of resolvins. The endogenous synthetic pathways to produce E-series resolvins (blue), D-series resolvins (orange) and T-series resolvins (green). PUFA, polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; COX-2, cyclooxygenase-2; LOX, lipoxygenase; P450 cytochrome P450 (Liu et al., 2022; Recchiuti et al., 2019; Rodriguez and Spur, 2020; Serhan and Levy, 2018; Serhan et al., 2022). This Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

4. Resolvins in diseases of the respiratory system

Resolvins have displayed potent bioactivities in various experimental disease models (Serhan and Levy, 2018). Experimental models of respiratory diseases have provided further insight into the molecular and cellular bioactivities of resolvins in pulmonary (patho)physiology (Fig. 3). The following sections will provide an up-to-date analysis regarding the role of resolvins in several pathologies affecting the respiratory system.

4.1. Acute lung injury and acute respiratory distress syndrome

Acute lung injury (ALI) and its more severe form acute respiratory distress syndrome (ARDS) are syndromes characterized by overreactive acute inflammation towards infection or injury (Tsushima et al., 2009). Major causes of ALI/ARDS include aspiration of gastric content, sepsis, repeated blood transfusion, inhalation injury, pancreatitis, and trauma. The clinical course varies with certain patients recovering after 1–2 weeks, while others experience an extended disease course with prolonged mechanical ventilation. ALI/ARDS may cause progressive worsening of the respiratory system by vascular and alveolar damage, which causes extravasation of serum proteins and over time pulmonary edema formation. Lung endothelial and epithelial injury leads to flooding of airspaces with protein-rich fluid, causing activation of alveolar macrophages and release of chemokines and cytokines. Attracted neutrophils migrate into alveoli and produce oxidants and proteases that increase tissue damage. Additionally, macrophage production of cytokines leads to extracellular matrix production by fibroblasts leading to pulmonary fibrosis.

Research has shown that for resolving lung injury, simply removing the injury causing agents is insufficient, but rather the elimination of apoptotic neutrophils, resolution of protein rich plasma and remodeling of matrix is important (Tsushima et al., 2009). SPMs have been shown to be important factors in resolving ALI/ARDS (Luo et al., 2022; Molaei et al., 2021). Both *in vivo* and *in vitro* studies of ARDS show that exogenously administered RvE1 upregulated epithelial sodium channel (ENaC) expression responsible for restoring the osmotic gradient required for reabsorbing pulmonary edema fluid (Luo et al., 2022). Additionally, they showed that RvE1 counteracted decreased Na^+/K^+-ATPase expression, which thereby restored the ability of alveolar epithelial cells to reabsorb edema fluid. Surprisingly, these effects were shown independent of $Chemerin_1$ or BLT1. As a result, RvE1 reduced pulmonary edema, improved lung injury, and improved survival rate in rats with lipopolysaccharide (LPS)-induced ARDS. In several *in vivo* models of ALI/ARDS, RvD1 administration reduced leukocytes and cytokines, proposedly due to downregulating inflammatory transcription factors such as nuclear factor-κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3) (Molaei et al., 2021; Shinohara et al., 2014; Zhuo et al., 2018). Additionally, decreasing NF-κB caused less expression of cluster of differentiation (CD) proteins such as CD41 on platelets, preventing neutrophil-platelet interactions to drive inflammation. Furthermore, *in vitro* studies with LPS-stimulated monocytes showed that RvD1 and RvD2 induced phosphorylation of glycogen synthase kinase 3 beta (GSK3β), leading to a reduction of pro-inflammatory mediators (Gu et al., 2016). Other downstream processes resulting from RvD1 binding to ALX/FPR2 include increasing production of antioxidant compounds such as superoxide dismutase to combat reactive oxygen species, decreasing fibrotic mediators such as transforming growth factor-β1 (TGF-β1) to prevent fibrosis and increasing the presence of Na^+/K^+-ATPase and ENaC in epithelial cells to reduce alveolar fluid collection (Molaei et al., 2021; Wang et al., 2011, 2014; Zheng et al., 2018). Due to its pro-resolving and anti-inflammatory effects, *in vivo* RvD1 treatment has been shown to improve bacterial clearance, reduce pulmonary edema and improve survivability (Molaei et al., 2021).

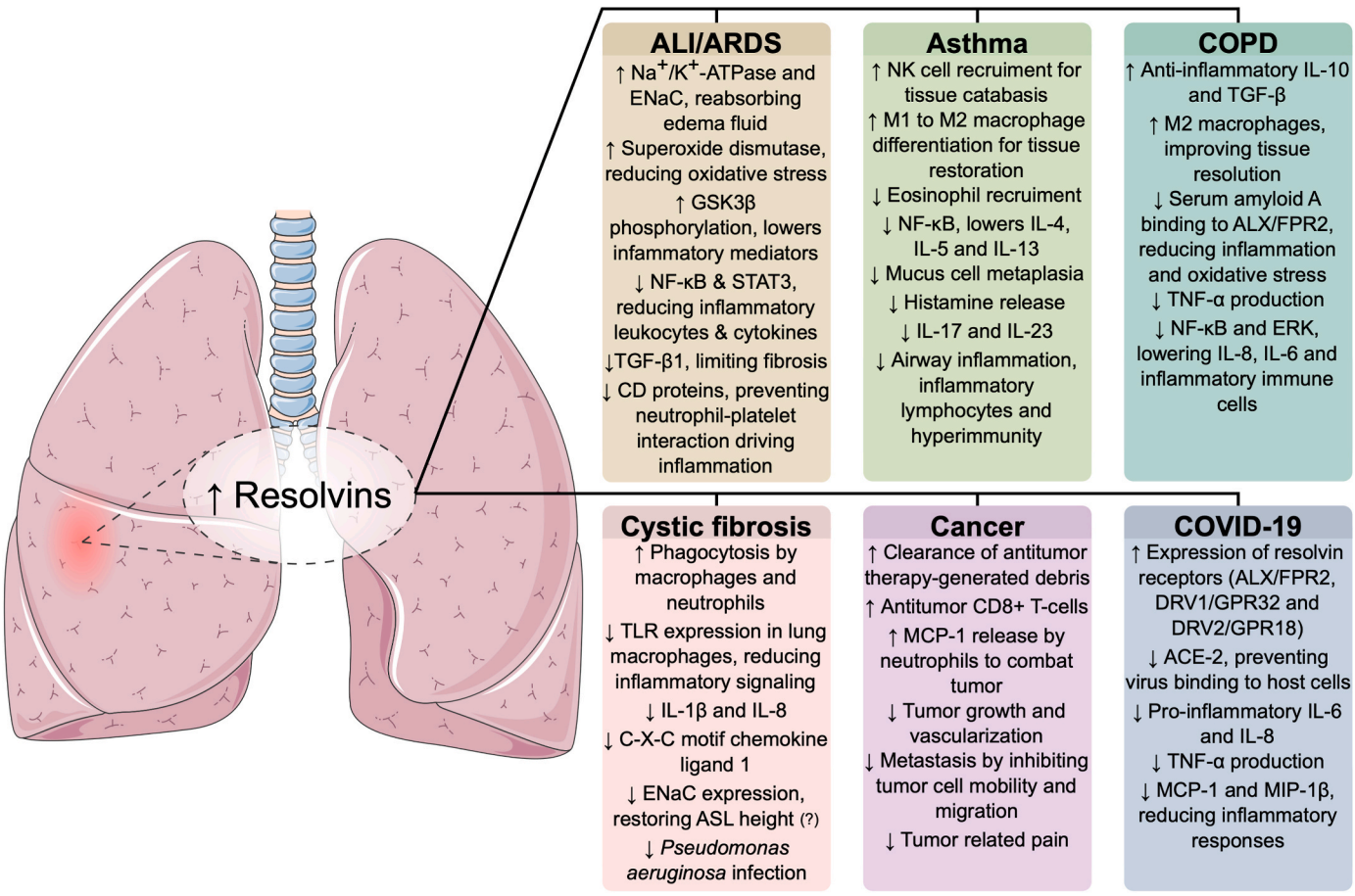

Fig. 3. Overview of the beneficial effects of resolvins in pulmonary diseases, ↑ = increased; ↓ = decreased. This Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

4.2. Asthma

Asthma is a heterogenous chronic respiratory disorder that causes coughing, wheezing, tightness in the chest and shortness of breath (Hammad and Lambrecht, 2021). The main feature of asthma is airway obstruction due to reduced airway diameter. Asthmatic symptoms are caused by airway inflammation triggering processes such as mucus formation, airway wall remodeling and airway hyperresponsiveness. A subset of patients with severe forms of asthma are unresponsive to corticosteroid therapy (Hammad and Lambrecht, 2021; Tliba and Panettieri, 2019), thus alternative therapies are required. Complex interplays between environmentally triggered epithelial cells and immune cells like eosinophils, neutrophils, DCs, lymphocytes, and innate lymphoid cells play a role in the development of the previously mentioned symptoms (Hammad and Lambrecht, 2021). Asthma is classified into type 2 (T2)-high asthma, which is mostly eosinophilic and T2-low asthma that is non-eosinophilic, commonly neutrophilic and metabolic. The T2-high classification is directed through T-helper 2 (Th2)-related cytokines such as IL-5, IL-13, and IL-4. The T2-low variant is less understood, with variable occurrence of both T2 and T1/T3 immunity, but mediators such as IL-1β and neutrophils appear to have a consistent role.

Many patients with uncontrolled inflammatory responses in the respiratory system show defective generation of SPMs, including clinically severe asthma (Levy, 2012). This suggests that chronic inflammation in asthma may result from defective resolution. Bronchoalveolar lavage (BAL) fluids of chicken ovalbumin-sensitized mice, utilized as *in vivo* models of allergic airway inflammation, showed that administration of RvD1 decreased eosinophil levels of IL-5, IL-13, and IL-4, proposedly due to reduced NF-κB (Rogerio et al., 2012). Thus, RvD1 may prevent the development of Th2 adaptive inflammation induced in many asthmatics. Furthermore, intravenous administration of RvE1 during the resolution phase accelerated clearing of mucus metaplasia, airway inflammation and reduced airway hyperreactivity together with reduction of IL-17 and IL-23 (Haworth et al., 2008, 2011). Previously, studies investigating IL-17 inhibition in lung disease led to inconsistent results in mouse models and negative trial results in humans (Hammad and Lambrecht, 2021). Therefore, more studies regarding the exact role of IL-17 and RvE1 treatment may be required. The bronchoprotective actions of RvE1 could also be partially related to activation and recruitment of NK cells which highly express the RvE1 receptor Chemerin$_1$ and appear important for tissue catabasis (Haworth et al., 2011).

A recent study showed that newborn mice may prenatally develop predisposition to asthma due to maternal exposure to noxious air particles, and that asthmatic symptoms of this offspring could be significantly reduced with intranasal delivery of RvE2 (Ramar et al., 2023). This indicates both substantial environmental effects in predisposition to asthma and that resolvins can be beneficial in reducing disease burden. Another study indicated that RvE3 administration in a murine asthma model featuring house dust mite-induced airway inflammation reduced levels of IL-5, IL-4, IL-13, IL-17 and IL-23 in the BAL fluid (Sato et al., 2019). RvE3 administration during the resolution phase resulted in decreased eosinophil recruitment, mucus cell hyperplasia, inflammation and airway hyperresponsiveness. Other murine model studies showed that intravenous administration of RvD1 decreased IL-5 and IL-17, eosinophils, lymphocytes and airway hyperresponsiveness (Rogerio et al., 2012). Furthermore, RvD1 stimulates M1 to M2 macrophage differentiation which can play a role in lung tissues restoration (Hsiao

et al., 2013). Additional findings include decreased release of histamine by RvD1 and RvD2 and increased phagocytosis of alveolar macrophages, indicating they may enhance clearance of apoptotic immune cells located in alveoli (Martin et al., 2012). Together, these findings indicate that resolvins may provide therapeutic potential in asthmatic patients.

4.3. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a major health concern causing disability and death and is caused by noxious exposures such as tobacco smoke, ambient air pollutants and previous lung infections together with social and genetic factors (Christenson et al., 2022). Symptoms include persistent airflow obstruction with coughing, sputum, increased susceptibility to infections and progressive dyspnea. The pathogenesis of COPD includes a crucial role of macrophages and neutrophils, which are known contributors to chronic inflammation and the development of small airway remodeling and emphysema. Emphysema is caused by protease-induced tissue degradation. The major protease involved is matrix metalloproteinase 12 (MMP12) produced by macrophages, but neutrophil elastase and other proteinases may also contribute to COPD development. Pulmonary macrophage accumulation occurs at least partially through resistance to apoptosis induced by smoking. Furthermore, macrophages associated with COPD show decreased phagocytosis of apoptotic cells and bacteria which further stimulates inflammation. Current treatments solely alleviate symptoms and once emphysema and chronic bronchitis develop, COPD progression may ensue despite patients stopping tobacco use (Hsiao et al., 2015).

Diets with omega-3 PUFAs have shown improvement of COPD symptoms (Shahar et al., 1994), indicating potential beneficial roles of SPMs in the respiratory system. Furthermore, levels of RvD1 have been shown to decrease in BAL fluid and serum of COPD patients (Croasdell et al., 2015), suggesting SPM signaling may be dysregulated in COPD. During *in vivo* studies, administration of the 17R epimer of RvD1 decreased acute cigarette smoke induced inflammation, reduced oxidative stress, and accelerated inflammatory resolution (Hsiao et al., 2015). On a molecular level, RvD1 administration increased IL-10 levels, an anti-inflammatory cytokine normally reduced in COPD. Conversely, a reduction of inflammatory macrophages, neutrophils, and inflammatory cytokines such as IL-8 was observed. These effects may be explained by RvD1 decreasing proinflammatory signaling by epithelial cells through blocking of ERK and NF-κB pathways (Hsiao et al., 2015; Molaei et al., 2021). Additionally, RvD1 may reduce inflammatory responses of serum amyloid A by competing for binding with ALX/FPR2 (Hsiao et al., 2015). The previously mentioned role of RvE3 and RvE1 to reduce airway inflammation in asthma through IL-23 and IL-17 reduction also are of interest for COPD (Haworth et al., 2008, 2011; Sato et al., 2019), since there is a frequent co-occurrence of these diseases with asthma being an early age risk factor for developing COPD (Christenson et al., 2022). *In vitro* studies of human alveolar macrophages showed that RvD1 and RvD2 reduced pro-inflammatory tumor necrosis factor alpha (TNF-α) production, with RvD2 also significantly dampening IL-6 and enhancing phagocytosis of *E. coli* (Croasdell et al., 2015). These results were found in both macrophages from COPD and non-COPD patients. Furthermore, RvD1 and RvD2 reduced proinflammatory cytokines, the ratio of pro-inflammatory M1 vs pro-resolving M2 macrophages and oxidative damage while simultaneously increasing anti-inflammatory TGFβ production and phagocytosis in human alveolar macrophages treated with cigarette smoke extract. Thus, these studies show that resolvins could therapeutically target harmful signaling pathways in chronic inflammation and promote re-establishment of homeostasis, thereby preventing COPD pathogenesis.

4.4. Cystic fibrosis

Cystic fibrosis (CF) is a recessive genetic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene which encodes the CFTR chloride channel (Briottet et al., 2020). While CF is systematic and can affect multiple organs, most morbidity and mortality is related to the disease affecting the lungs. The primary function of CFTR is transport of chloride from cytosol to lumen. Additionally, CFTR regulates ENaC activity in the epithelial membrane. Both the CFTR channel and ENaC regulate the formation of the dehydrated airway surface liquid (ASL), which forms the initial innate defensive line by trapping and neutralizing exogenous particles which can subsequently be removed by ciliated cells from the airways. The disrupted transport of ions in CF reduces ASL height, leading to reduced ciliary movement and increased mucus plugging. This provides pathogens, especially bacteria, with a medium where they can more rapidly proliferate. In CF, inflammation of the airways begins early in life and can be present even when no microbials are detectable. Furthermore, the inflammatory reaction during infections is excessive relative to the burden of infection and non-resolving. Current anti-inflammatory therapy like ibuprofen has shown meagre clinical benefit in CF patients (Recchiuti et al., 2019). CFTR modulators (potentiators and modulators) have allowed the acquirement of CFTR function in patients with certain CF mutations. However, while studies have shown that CF modulators reduced the presence of CF related pathogens, no changes in inflammation were observed. Thus, modulators alone are not sufficient to eliminate chronic inflammation. Additional CF modulator studies were able to indicate a decrease of inflammatory markers, but still at supranormal values (Hisert et al., 2017). Furthermore, these investigations showed that while initially CF related pathogens decreased, they re-increased after the first year of CF modulator treatment. Therefore, alternative therapeutics that target excessive inflammation and promote resolution in CF are required.

The levels of resolvins in the airway of CF patients have been correlated with lung function (Eickmeier et al., 2017). Additionally, lower expression of the 15-LOX responsible for resolvin production was observed in both CF mice models and BAL fluid from CF pediatric patients (Karp et al., 2004; Ringholz et al., 2014). These findings may indicate that abnormal SPM biosynthesis contributes to CF. *In vitro* studies have shown that RvD1 reduces bacterial burden of *Pseudomonas aeruginosa* (*P. aeruginosa*), a pathogen commonly present in CF, by increasing macrophage and neutrophil phagocytosis (Codagnone et al., 2018). Additionally, RvD1 reduces toll-like receptor (TLR) expression in lung macrophages, thus dampening danger signaling that can drive inflammation. Other *in vitro* observations of RvD1 administration include reduced IL-8 secretion, reduced leukocyte infiltration and a restoration of ASL height through decreasing ENaC (Codagnone et al., 2018; Ringholz et al., 2018). The latter finding contradicts RvD1 increasing ENaC in ALI/ARDS murine models (Liu et al., 2022). These paradoxical findings may indicate that RvD1 treatment can have differential effect depending on the pathology and/or disease model and warrants further investigation. *In vivo* studies of *P. aeruginosa* infected mice treated with RvD1 showed decreased neutrophils, IL-1β and the C-X-C motif chemokine ligand 1 in their lungs (Codagnone et al., 2018).

Human CF studies regarding the treatment with SPM are lacking, but studies have shown inverse correlation of pro-inflammatory IL-6 and IL-8 with endogenous RvD1 in CF patient sputum (Isopi et al., 2020). Additionally, a phase IIa clinical trial showed that lenabasum, a cannabinoid-derived small molecule drug shown to increase SPM production including RvD1, was able to reduce IL-8, elastase, neutrophils in sputum and reduce the risk of acute worsening of respiratory symptoms in CF (Chmiel et al., 2021; Motwani et al., 2018a). Thus, this showcases that therapeutics targeting resolution pathways may be effective for treating chronic inflammatory disease.

4.5. Cancer

Cancer therapy is focused on effectively killing tumor cells to reduce tumor burden and often relies on utilizing broadly cytotoxic

chemotherapies, irradiation, surgery, or more specific inhibition of certain molecular pathways (Panigrahy et al., 2019). However, tumor treatment can be regarded as a double-edged sword as it is observed that surgery, chemotherapy and irradiation can induce release of pro-inflammatory and pro-angiogenic cytokines that can promote escape from cancer dormancy, leading to tumor reoccurrence at metastatic sites. The lung is considered one of the most common locations for the development of secondary tumors, which can reach the lungs though either lymphatic or hematogenous routes or by direct invasion, complicating oncological treatment (Jamil and Kasi, 2022). Therefore, means to prevent metastasis of tumors towards the lung and additional metastatic sites during treatment while retaining tumor eradicative effects is of high interest.

Studies utilizing *in vivo* Lewis lung carcinoma models (LLCs) showed the pre-operative administration of exogenous RvD2, RvD3 or RvD4 prevented metastasis and led to a 50–80% increase of survival 37 days post-resection compared to control (Panigrahy et al., 2019). The most prominent increase of survival and prevention of metastasis was observed by pre-operative (2 h prior) administration of RvD2, showing significant reduction of surgery-induced dormancy escape. Thus, pre-operative treatment with resolvins can improve survival rate in cancer and prevent the reoccurrence of tumors. Additionally, RvD2 treatment showed an increase of $CD8^+$ T-cells in mice lung tissue, indicating resolvins may also stimulate antitumor activity.

Additional studies show that administration of RvD1, RvD2 and RvE1 accelerate removal of antitumor therapy-generated debris by increasing macrophage phagocytosis and reduced proinflammatory molecules (Sulciner et al., 2017). These effects inhibited debris-stimulated primary tumor growth and lung metastasis in several mouse tumor models including lung adenocarcinoma and LLC. While promising, some studies suggest that pro-immunogenic tumor debris caused by anti-tumor treatment can conversely induce endogenous antitumor immunity. Thus, more studies may be needed to understand the specific conditions in which therapeutically formed tumor debris activates or suppresses antitumor immunity.

In non-debris tumor models containing solely living tumor cells, RvD1, RvD2 and RvE1 treatment inhibited primary tumor growth equivalently to chemotherapy (Sulciner et al., 2017). The antitumor activity of resolvins in these *in vivo* models was shown to be receptor dependent as knock out of $Chemerin_1$, DRV2/GPR18, ALX/FPR2 accelerated both debris and non-debris related tumor growth. Interestingly, research has shown that utilizing anti-$Chemerin_1$ antibodies to activate the RvE1 receptor are therefore also effective at stimulating resolution and reducing cancer burden (Trilleaud et al., 2021). While these RvE1 receptor antibodies have thus far only been tested in murine models of colon cancer, this effect may be found in other forms of cancer including lung malignancies. For example, another study in murine models of lung cancer also indicated that RvE1 administration reduced tumor size, metastasis and vascularization (Kantarci et al., 2022). Furthermore, they showed that RvE1 co-administration may enhance therapeutic actions of cisplatin, allowing for reduced dosing of chemotherapeutic. Additional resolvin studies have shown the anti-tumor activity of RvD1 by stimulating anti-tumor neutrophil responses (Mattoscio et al., 2021). RvD1 induced the release of monocyte chemoattractant protein-1 (MCP-1) by neutrophils, which stimulated anti-tumor monocyte recruitment causing tumor reduction. Furthermore, RvD1 and RvD2 have been shown to suppress lung tumor cells acquiring mesenchymal features required for mobility and migration away from the primary tumor site (Lee et al., 2013). In other cancer types, RvE1, RvD1 and RvD2 have shown to have analgesic effects in tumor-associated pain and prevent transition of hepatitis towards cancer (Khasabova et al., 2020; Kuang et al., 2016; Ye et al., 2018). The latter indicates that resolvins may also prevent chronic inflammation to result in cancer development (Schett and Neurath, 2018).

4.6. COVID-19

Coronavirus disease (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has been classified as a pandemic by the World Health Organization (Ferreira et al., 2022; Palmas et al., 2021). SARS-CoV-2 infects lung epithelial cells and immune cells such as macrophages, enabling the pathogen to trigger a hyperinflammatory state. The COVID-19 pandemic has been one of the greatest health problems of the 21st century with enormous global morbidity and mortality, causing 2.2 million deaths (Molaei et al., 2021; Palmas et al., 2021). COVID-19 infections show primary symptoms such as coughing, fever and dyspnea, fatigue and headaches (Ferreira et al., 2022; Molaei et al., 2021). However, the disease can also be associated with more exorbitant symptoms such as acute kidney injury, pneumonia, and ARDS. Severe COVID-19 cases are linked to non-resolving inflammatory responses and show that the disease can cause systemic inflammation, sepsis, organ failure and even death (Ferreira et al., 2022; Recchiuti et al., 2021). Disease progression has proposedly been linked to the triggering of uncontrolled cytokine release due to activation of T cells, macrophages and humoral immune responses. Disease progression and severe COVID-19 disease is more likely in elderly and in patients with comorbidities as hypertension, respiratory disease, cardiovascular disease, or diabetes (Ferreira et al., 2022). Interestingly, obesity can contribute to the risk of SARS-CoV-2 infection and appears related to deficiency of SPMs.

Most COVID-19 infection studies have shown an increase of pro-inflammatory eicosanoids such as prostaglandins and LTB_4 (Archambault et al., 2021; Serhan et al., 2022). These could potentially drive and amplify uncontrolled pro-inflammatory cytokine release and excessive inflammation of the lungs during COVID-19 infections. Plasma lipid mediator profiles in COVID-19 patients revealed that aside from pro-inflammatory lipid mediators, SPMs were also upregulated in patients with moderate to severe disease, including RvD1 and RvT3 (Palmas et al., 2021). However, in patients with critically ill disease, both pro-inflammatory lipid mediators and SPMs were significantly reduced, suggesting that disruption of lipid mediators may play a role in disease progression. Furthermore, within critically ill patients, non-surviving patients had significantly lower levels of SPMs compared to survivors. Interestingly, consumption of the resolvin omega-3 precursors, has been implicated to improve the treatment and recovery of patients with COVID-19 infections (Nursyifa Fadiyah et al., 2022). *In vitro* studies in non-CF and CF human macrophages exposed to the SARS-CoV-2 virion spike 1 glycoprotein (S1) showed increased chemokine levels (Recchiuti et al., 2021). This included IL-8 and MCP-1, macrophage inflammatory protein 1-beta (MIP-1β) and MIP-1α in both macrophage cell types and additionally IL-6 and TNF-α in non-CF macrophages. Interestingly, while exposure to S1 increased RvD1 production in CF macrophages, it simultaneously decreased resolvin receptor expression levels (ALX/FPR2, DRV1/GPR32 and DRV2/GPR18) in both non-CF and CF macrophages. Treatment with exogenous RvD1 and RvD2 reverted the suppressive action of S1 on receptor expression. Furthermore, resolvin treatment stopped macrophage inflammatory responses induced by S1, including production of IL-8, TNF-α, IL-6, MCP-1 and MIP-1β. Reduction of MIP-1α occurred selectively in CF macrophages with RvD2 treatment. Finally, additional studies have indicated that RvD6 isomers are able to reduce the expression of angiotensin converting enzyme 2 (ACE-2) to prevent coronavirus spike protein binding in injured cornea through ACE-2 (Pham et al., 2021). Together, these findings suggest that treatment with resolvins may prevent excessive inflammation and pathogen infection of host cells, which could aid in preventing severe COVID-19 and ameliorate disease symptoms.

5. Clinical use of SPMs

While the use of exogenously administered resolvins and other SPMs have been researched in a wide array of lung diseases and other

pathologies, most research thus far has been preclinical. Following the discovery of resolvins by Serhan et al. (2002), a patent was filed that was licensed to the company Resolvyx (Blaudez et al., 2022). Initially, the company primarily targeted respiratory disorders such as CF and asthma, but over the years it reoriented towards dry eyes treatment for reasons unknown. Resolvyx tested the safety risks of an orally delivered resolvin formulation dubbed RX-10001 in a phase I clinical trial based on 300 mg tablets (Hesselink et al., 2016). However, clinical development of RX-10001 seems to have stopped as the company shifted development to a more stable synthetic RvE1 analog called RX-10045. After promising *in vivo* results, the resolvin analog was assessed during two phase II clinical trials, one for individuals with dry eyes in 2013 and a trial for ocular inflammation and pain following cataract surgery in 2014 (Blaudez et al., 2022). Treatment involved topical administration of 0.05% or 0.1% ophthalmic solutions of RX-10045. While clinical trials have been completed, results remain unknown, which may indicate findings were not as promising as initially expected. More recently, RX-10045 has been licensed by Auven Therapeutics in 2015 and entered phase-II clinical trials for postoperative pain and inflammation (Hesselink et al., 2016). Additionally, the compound entered pre-clinical assessment for diabetic macular edema and macular degeneration. In academic research, a clinical study utilizing UV-killed *E. coli*-triggered skin inflammation showed that treatment with SPMs (lipoxin B_4, RvE1, RvD2 and 17R-RvD1) 4 h after exposure was pro-resolving, significantly reducing the infiltration of neutrophils without negatively affecting the clearance of bacterial endotoxins (Motwani et al., 2018b).

Aside from resolvins, there are data available from clinical studies regarding the use of other SPMs. A clinical trial with the topically stable lipoxin analog 15(R/S)-methyl-LXA(4) for treating infantile eczema indicates that this analog produced comparable effects to topical corticosteroid treatment and reduced severity of eczema and improved quality of life with no safety concerns (Wu et al., 2013). In the context of respiratory diseases, two lipoxin analogs, 5(S),6(R)-LXA4 methyl ester and BML-111 were diluted into a normal saline inhalation solution for treating asthma (Kong et al., 2017). Treatment showed improved pulmonary function superior to treatment with the inhaled corticosteroid budesonide with no observed clinical adverse events. While these findings concerned another class of SPMs, results may be extrapolated to resolvins, showing that stable forms of resolvins combined with pulmonary delivery could be explored as clinical treatment strategies against respiratory diseases.

6. Discussion

The human body must react to infections, injuries, and noxious stimuli such as toxins, allergens and irritants to preserve health (Nathan and Ding, 2010). Notably, the respiratory system is potentially exposed to harmful agents at each breath, thus requiring adequate defense mechanism. During insult exposure, the host responds by initiating an acute inflammatory response that must subsequently be resolved to re-establish homeostasis and prevent excessive and chronic inflammation. Perturbing inflammatory resolution is considered a crucial pathophysiological process in the development of many diseases. This includes respiratory pathologies, where diseases such as COPD, asthma, CF and cancer have been associated with a chronic inflammatory tissue state that is inadequately resolved (Eickmeier et al., 2017; Levy, 2012; Panigrahy et al., 2019; Shahar et al., 1994). Dysregulated acute inflammatory responses have also been associated with defective resolution such as in ALI/ARDS (Luo et al., 2022; Molaei et al., 2021). Resolvins derived from DHA, DPA and EPA can be produced at inflammatory tissue sites, acting at picogram to nanogram ranges on GPCRs expressed on cells in the inflammatory environment, including macrophages, neutrophils, lymphocytes, endothelial and epithelial cells (Serhan et al., 2014). Resolvins have been implicated in modulating disease and re-establishing tissue homeostasis after inflammation. Decreased levels of SPMs have been observed in many respiratory diseases (Croasdell et al., 2015; Levy, 2012; Palmas et al., 2021), indicating that resolvin production is potentially impaired due to pathophysiological processes which may contribute to both disease exacerbation and lack of disease resolution. Several studies have revealed that exogenous resolvin administration reduces inflammation and induces tissue restoration (Hsiao et al., 2015; Levy, 2012; Panigrahy et al., 2019). These studies demonstrate that resolvins are important mediators to reduce disease burden and improve survival. Thus far, several therapeutic strategies have been explored to utilize resolvins and their pro-resolution pathways to modulate respiratory disease. These can be summarized to (i) administering exogenous resolvin analogs, (ii) inducing endogenous production of resolvins, either with drugs or supplementation of omega-3 PUFA precursors, (iii) targeting the signal transduction pathway of resolvins with alternative agents to induce pro-resolving bioactions and, (iv) utilizing endogenous resolvins levels as biomarkers for disease severity and progression.

The use of synthetically produced resolvins as therapeutics to treat respiratory diseases have shown promising preclinical results (Hsiao et al., 2015; Levy, 2012; Palmas et al., 2021; Panigrahy et al., 2019). However, pro-resolving therapies are still in their infancy and some limitations must be resolved for successful clinical application. Most notably, resolvins are considered unstable, quickly metabolized and degraded. This limits bioavailability of the drug and has led to the impracticable scenarios such as repetitive administration to assess therapeutic effects during experimentation (Cherpokova et al., 2019). More stable analogs of SPMs have been produced, including RvE1. Stagnated clinical trials studying this synthetic analog may however indicate that bioavailability requires further improvement. While clear clinical results in the form of academic reports are lacking, the RvE1 analog RX-10045 was reportedly difficult to formulate; allegedly unstable, sensitive to light and relatively prone to breakdown at room temperature which may have contributed to potential unfavorable clinical results (Hesselink et al., 2016). Others studies have also mentioned the sensitivity of resolvins to light, heat and oxidation and additionally limited and costly supply (Liu et al., 2022). Nevertheless, other methyl-ester prodrugs of SPMs, such as lipoxin analogs were effective at treating asthma in a pilot study (Kong et al., 2017). Thus, whether the formulation was the prime reason investigations of RX-10045 appears stagnated remains uncertain. Other stable analogs of resolvins have been produced such as benzo-RvE2 and benzo-RvD1 analogs and a 19-p-fluorophenoxy-RvE1 analog that resisted metabolic inactivation and improved *in vivo* efficacy (Serhan et al., 2022), showing promise for the clinical potential of resolvins. Nevertheless, it seems that most studies primarily focused on elucidating the role of resolvins in pathophysiology of experimental models, causing insufficient attention regarding innovative formulation of these compounds. Focusing on pharmacokinetics and drug delivery may be required to produce effective treatments for pulmonary diseases. For example, the use of innovative liposomes in aerosolization devices for pulmonary delivery may be investigated. These have been both clinically approved and are ongoingly tested in clinical trials for respiratory delivery of anti-cancer and antibacterial drugs (Mehta et al., 2020). Liposomes and direct pulmonary delivery may improve stability of resolvins and give gradual drug release directly at the pathological source, therefore improving drug availability. Exploration of various pulmonary delivery systems such as dry-powder inhalers and nebulizers together with dose finding could support optimal clinical drug translation.

Regarding future research with exogenously administered resolvins, RvD1 and RvE1 appear to be most extensively studied and show a plethora of promising results in respiratory diseases (Hisada et al., 2017; Hsiao et al., 2015; Levy, 2012; Luo et al., 2022; Molaei et al., 2021; Panigrahy et al., 2019; Recchiuti et al., 2021; Sulciner et al., 2017). Both subtypes commonly share favorable results within a disease such as in asthma, ALI/ARDS and cancer. This broad effectivity makes them ideal drug candidates. Nevertheless, one study indicated that solely RvD1 reduced *P. aeruginosa* infections *in vivo* successfully with unfavorable

RvE1 results (Codagnone et al., 2018). Therefore, RvE1 may not be suitable for dealing with CF related *P. aeruginosa* infections and indicates that careful subtype selection for each disease will be required in conjunction with optimizing resolvin stability and administration. RvD1, which targets ALX/FPR2 and GPR32, appears broadly effective in respiratory diseases, but it remains interesting to compare its effectiveness against other resolvin subtypes for different diseases. Additional resolvin subtypes such as the more recently discovered RvE4 and RvTs appear less studied as therapeutics, potentially leading to biased selection of earlier subtypes without proper comparison. RvT expression profile alterations have been observed in COVID-19 infected patients (Palmas et al., 2021), indicating that these could also serve as therapeutic agents for treating lung disease. Thus, more *in vitro* and *in vivo* studies focusing on integral comparison in treatment efficacy of different resolvin subtypes would be interesting to explore in the future. Additionally, the unique signaling pathways and receptors within resolvin subtypes warrant investigating concomitant subtype administration. While sharing many downstream pro-resolving effects, they may work synergistically in achieving resolution through distinct signaling pathways.

Drugs such as aspirin, statins and lenabasum have been shown to stimulate endogenous production of resolvins and to potentially reduce disease burden (Chmiel et al., 2021; Serhan and Levy, 2018; Serhan et al., 2022). Discovering aspirin-induced SPM production explained mechanisms for the well-appreciated functioning of aspirin as not only an anti-inflammatory but also a pro-resolving drug (Serhan and Levy, 2018). This distinguishes it from NSAIDs which typically lengthen the time until resolution. Therefore, the effects that drugs may have on SPM production should be taken into consideration for the development of drugs that are resolution-friendly instead of resolution-disruptive. The discovery of additional compounds that boost endogenous resolvin production could aid in overcoming disrupted resolvin production occurring in pulmonary disease. Supplementation of omega-3 PUFAs has led to an interest in immunonutrition to reduce disease burden. Nevertheless, clinical trials utilizing omega-3 PUFA supplementation have given mixed results. Maternal omega-3 supplementation has been associated with reduced incidence of asthma and respiratory infections in infants (Serhan and Levy, 2018). Omega-3 supplementation has also been implicated to accelerate recovery in COVID-19 patients (Nursyifa Fadiyah et al., 2022). However, evidence regarding clinical benefits of omega-3 supplementation in asthma is weak (Barnig et al., 2018). Furthermore, the levels of omega-3 PUFAs required for adequate production of SPMs are unknown since dietary consumption targets of omega-3 PUFAs that include SPM production as a criterion do not exist. Ultimately, improved understanding regarding omega-3 PUFA dosing and responses in the form of transformation to resolvins in the airways is needed to establish well-defined clinical benefits.

Beneficial anti-Chemerin$_1$ antibody treatment in oncology research implicates that other forms of drugs with potentially superior pharmacokinetics could serve as alternatives to resolvin analogs as pro-resolving therapeutics (Trilleaud et al., 2021). Recently, an ALX/FPR2 agonist (ACT-389949) was investigated during a phase I trial and appeared well tolerated and safe (Barnig et al., 2018; Stalder et al., 2017). However, its use as an immunoresolvent drug may be limited, as biomarker assessment indicated that ACT-389949 conversely induced transiently pro-inflammatory responses and swift desensitization of ALX/FPR2 (Stalder et al., 2017). Receptor agonists for ALX/FPR2 have been tough to produce since the dimerization state of the receptor is ligand-dependent which can cause differential signaling. Nevertheless, ALX/FPR2 remains a promising target as it enables activating key features of resolution. An increasing number of small molecules are being developed for this receptor, with another compound (BMS-986235) with pro-resolving effects recently completing phase I trials (Perretti and Godson, 2020). If FPR2/ALX signaling is further delineated through future ligand-receptor interaction studies, therapeutics such as antibodies and small molecules, which are already widely used, may hold promise over resolvins due to their generally superior *in vivo* stability. For several other resolvin subtypes, the receptor targets are currently ill-defined (Table 1), thus limiting drug development. Overall, studies to further understand receptor targets, binding mechanics and subsequent signaling cascades will be required for effectively targeting resolvin pathways with non-SPM based drugs.

Therapeutic use of resolvins and related signaling pathways is considered an immunoresolvent strategy rather than an immunosuppressive one that compromises host-defense. Nevertheless, aside from pro-resolving activities, resolvins also show concomitant anti-inflammatory properties (Serhan et al., 2014). Normally, endogenous resolvins are highly regulated due to their short half-life and local production at the inflammatory site, although some human tissues and fluids reveal constitutive expression of SPMs to a certain extent (Serhan and Levy, 2018). This tight regulation would be lost during systemic administration and in therapies with prolonged effects. Potentially excessive anti-inflammatory activities during systemic delivery may warrant a more long-term investigation of the pro-resolving therapeutics to assess whether unwanted effects arise such as susceptibility to novel infections, which could negatively impact their clinical use. It should be noted however that thus far, both pre-clinical and clinical studies of resolvins and other SPMs have indicated they are safe and well tolerated (Serhan et al., 2014). Furthermore, their administration may improve the clearance of ongoing infections rather that suppress them and may lower required antibiotic dosages.

7. Conclusion

This review summarizes the mechanisms behind inflammation and its resolution, resolvin biosynthesis and their targets, and ongoing research into pro-resolving therapeutic strategies with a focus on respiratory diseases. There are several studies confirming that disrupted inflammatory resolution plays a role in pulmonary disease pathophysiology and that resolvins can modulate this response to induce tissue homeostasis. Nevertheless, additional investigations are required to further elucidate the mechanistic actions of resolvins, and the efficacy and safety of novel resolution-based therapeutics with improved pharmacokinetics in both pre-clinical and clinical settings. Ultimately, the clinical success of therapeutic agents will depend on which drawbacks can be overcome, namely the stability of resolvin mimetics or the improper signaling of resolution by therapeutics of different origin such as small molecules. All things considered, resolvins, their receptors and their respective pathways exhibit promise for future therapeutics against respiratory diseases.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Data availability

No data was used for the research described in the article.

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